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10/752,423	01/06/2004	Erik Buntinx	29248/19	3783

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AMSTER, ROTHSTEIN & EBENSTEIN LLP
90 PARK AVENUE
NEW YORK, NY 10016

EXAMINER	
RAMACHANDRAN, UMAMAHESWARI	
ART UNIT	PAPER NUMBER
1617	
MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/752,423	BUNTINX, ERIK	
	Examiner	Art Unit	
	UMAMAHESWARI RAMACHANDRAN	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 November 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,10 and 64-67* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,10 and 64-67* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *11/12/2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The examiner notes the receipt of the amendments and remarks received in the office on 11/12/2008. Claims 1, 10 have been amended and claims 2-9, 11-63 have been canceled, and claims 64-67 have been added new. Claims 1, 10, 64-67 are currently pending and are being examined on the merits herein.

Response to Remarks

Applicants' acknowledges the provisional double patenting rejection of claims 1-4, 6-10 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 82-84, 100, 101 of copending Application No. 10/580,962. Accordingly, the rejection is maintained and given below for Applicants' convenience. The provisional double patenting rejection of claims 1, 9 over claims 1-4 and 42 of copending Application No. 10/984,683 in view of in view of Sanchez (U.S. 2002/0086899) is withdrawn due to the cancellation of claims 1 and 9 of the co-pending application. The rejection of claims 1, 7, 9, 10 under 35 U.S.C. 112, first paragraph is withdrawn due to the amendment of claim 1. Applicants' arguments regarding the rejection of claims 1, 7, 9, 10 under 35 U.S.C. 112, first paragraph and rejection of claims 1, 7, 9, 10 under 35 U.S.C. 103(a) as being unpatentable over Dipiperon (Applicant cited reference, manufacturer sheet) in view of Sanchez (U.S. 2002/0086899) have been fully considered and found not to be persuasive. ,The rejections are maintained and are given below for Applicants' convenience. Applicants' addition of new claims and amendments necessitated the new and modified rejections presented in this action. Accordingly, the action is made Final.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 10 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 82-84, 100, 101 of copending Application No. 10/580,962.

Claims 1, 10 of the instant application are drawn to a method of for treating a disease or disorder such as anxiety disorder comprising administering to a patient a compound such as pipamperone and a second agent, citalopram, a serotonin reuptake inhibitor.

Claims 82-84, 100,101 of the co-pending application ('962) teach a method for treating mood disorders or anxiety disorders comprising administering to a patient pipamperone, or a pharmaceutically acceptable salt thereof, in a dose ranging between 5 and 15 mg per day of the active ingredient, and administering said pipamperone simultaneously with, separate from or sequential to a second compound, to augment the therapeutic effect of said second compound or to provide a faster onset of the

therapeutic effect of said second compound, wherein said second compound is selected from the group consisting of: selective serotonin, nor-adrenaline and dopamine re-uptake inhibitors (SNDRI), selective serotonin and nor-adrenaline re-uptake inhibitors (SNRI) and selective serotonin re-uptake inhibitors (SSRI). The co-pending application further teaches escitalopram, fluoxetine etc to be a second agent.

Although the conflicting claims are not identical, they are not patentably distinct from each other because both teach a method of treatment of emotional disorders such as anxiety disorder comprising administering pipamperone and a selective serotonin reuptake inhibitor such as citalopram as a second agent.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 10, 64, 65 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The specification teach measuring pKi values of some test compounds and describes the foregoing pipamperone-citalopram treatment for depressive disorder clinical trial set up data but do not show any real data or examples of treating a disorder such as anxiety disorder administering to a patient a compound such as pipamperone and an SSRI compound. Also, there is no data in the specification showing the augmentation of therapeutic effect of Selective

Serotonin Reuptake Inhibitor (SSRI) or a faster onset of the therapeutic effect of said SSRI when the selective serotonin reuptake inhibitor is administered to the patient simultaneously with the administration of pipamperone. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The specification does not provide support to the subject matter of the claimed invention of treating an anxiety disorder comprising administering pipamperone in a daily dose ranging between 5 and 15 mg and an SSRI wherein said simultaneous administration of pipamperone and said SSRI augments the therapeutic effect of said SSRI or providing a faster onset of the therapeutic effect.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1, 10, 64-67 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dipiperon (Applicant cited IDS reference, manufacturer sheet) in view of Sanchez (U.S. 2002/0086899) and further in view of Broekkamp et al. (U.S. 6,150,353).

Dipiperon document teaches that pipamperone (dipiperon) is useful in the symptomatic treatment of serious forms of agitation and anxiety (p 1, Therapeutic indications). The reference teaches 40-80 mg doses for adults and 20 mg divided in two doses for children.

The reference does not teach a combination therapy with an SSRI such as citalopram in a method of treatment of anxiety.

Sanchez teach the use of escitalopram (s-enantiomer of citalopram, 40 mg/kg) in the treatment of neurotic disorders including anxiety disorder, social anxiety disorder etc. (See Abstract).

The reference Dipiperon document does not teach the amount of pipamperone to be 5 and 15 mg as the daily dosage range.

Broekkamp et al. teaches combination therapy comprising an antidepressant and an antipsychotic agent such as pipamperone. The reference teaches that antipsychotic agents such as pipamperone are administered in a suitable dose range of 0.001 mg to 25 mg per kilogram body weight, preferably in the range of 0.1 to 10 mg per kg/day in combination therapy with an antidepressant (col.3, lines 1-6, col. 5-6, and claims 1, 3 and 4). The reference teaches a pharmaceutical formulation comprising a combination of an antidepressant and an antipsychotic drug such as pipamperone in association with

one or more pharmaceutically acceptable carriers therefore and a process to make the formulation (col. 6, claims 5, 8 and 9).

It would have been obvious to one of ordinary skill in the art at the time of the invention to use pipamperone and citalopram in a method of treatment of a disease or a disorder such as anxiety disorder because of the teachings of Dipiperon and Sanchez. Diperon teaches the use of pipamperone in the treatment of anxiety disorder and Sanchez teaches the use of citalopram in the treatment of anxiety disorders. Hence one of ordinary skill in the art would have been motivated to use pipamperone and citalopram in a combination therapy for the treatment of a disease or a disorder such as anxiety disorder due to expectation of synergistic effects and therapeutic benefits as both the compounds have been shown to be useful in a method of treatment of condition like anxiety disorder. Regarding the daily dose of pipamperone in the composition as recited in claim 1, Broekkamp et al. teaches pipamperone in a combination therapy. The reference teaches administration of low doses of 0.001 mg to 25 mg per kg/day of pipamperone with an antidepressant in a combination therapy. Citalopram is a well known antidepressant drug (http://en.wikipedia.org/wiki/Citalopram). Hence it would have been obvious to one of ordinary skill in the art at the time of the invention to have administered a dose of 5 to 15 mg of pipamperone in a combination therapy along with an antidepressant such as citalopram from the studies of Broekkamp et al. One having ordinary skill in the art would have been motivated in administering such a low dose of 5 to 15 mg of pipamperone in treating an anxiety disorder in

expectation of success and also in achieving less side effects with lower dosage of the drug.

The references do not teach a pharmaceutical composition comprising pipamperone and a selective serotonin reuptake inhibitor drug such as citalopram.

It would have been obvious to one of ordinary skill in the art at the time of the invention to formulate pipamperone and citalopram in a single pharmaceutical formulation because both the drugs are taught in the prior art to be useful in treating anxiety disorder. One of ordinary skill in the art would have been motivated to incorporate the both the agents herein in a single pharmaceutical composition because combining the agents herein each of which is known to be useful to treat anxiety disorders individually into a single composition useful for the very same purpose is *prima facie* obvious. See *In re Kerkhoven* 205 USPQ 1069. It is well known that it is *prima facie* obvious to combine two or more ingredients each of which is taught by the prior art to be useful for the same purpose in order to form a third composition which is useful for the same purpose. The idea for combining them flows logically from their having been used individually in the prior art. *In re Sussman,* 1943 C.D. 518; *In re Pinten,* 459 F.2d 1053, 173 USPQ 801 (CCPA 1972); *In re Susi,* 58 CCPA 1074, 1079-80; 440 F.2d 442,445; 169 USPQ 423, 426 (1971); *In re Crockett,* 47 CCPA 1018, 1020-21; 279 F.2d 274, 276-277; 126 USPQ 186, 188 (1960). Thus, since the individual components are known to be used individually in the art for the same purpose, then to use them together as such or in one composition is obvious. Also, it would have been obvious to one of ordinary skill in the art at the time of the invention to formulate

pipamperone and citalopram in a single pharmaceutical formulation from Broekkamp et al.'s teachings. The reference teaches a combination therapy comprising an antidepressant and an antipsychotic drug such as pipamperone and also teach a pharmaceutical formulation comprising an antipsychotic agent and an antidepressant. Thus the reference teaches that pipamperone can be combined with another antidepressant and is useful in a combination therapy. It would have been obvious to one of ordinary skill in the art at the time of the invention to have made a pharmaceutical composition comprising pipamperone and another antidepressant such as citalopram. One having ordinary skill in the art would have been motivated in such a formulation because of expectation of success.

The references do not teach the administration of SSRI as simultaneous and pipamperone augments the therapeutic effect of said SSRI. It would have been obvious to one of ordinary skill in the art at the time of the invention that drugs useful for the same disorder or disease can be given as a combination therapy and it is well known that in combination therapy drugs are administered simultaneously or sequentially as the prior art (Dudley et al. (US 2004/0002482)) teaches citalopram and pipamperone can be used in combination therapy in a method of treatment of depressive disorder. Accordingly in a combination therapy of pipamperone and citalopram when SSRI is administered simultaneously, after administration of pipamperone the effects will be the same as claimed (augmentation of therapeutic effects of SSRI).

Response to Arguments

Applicant's arguments with respect to 112(1) and 103 (a) rejection of the claims have been considered and found not to be persuasive.

Applicants' state that experimental examples are presented in related U.S. Patent Application Nos. 10/984,683 [US 2005/0203130] and 10/580,962 [US 2007/0078162]. The Examples show the advantages of using pipamperone with citalopram to treat depression (Example 3), obsessive-compulsive disorder (Example 4), and panic disorder (Example 5). Obsessive- compulsive disorder and panic disorder are types of anxiety disorders. In response, the applications 10/984, 683 and 10/580,962 are CIP applications of 10/752,423, the instant application. The examples provided in those applications does not satisfy the written description requirement of the instant application. Applicants' state that the specification provides an explanation for the advantage of the combined treatment in paragraphs 0042-0045. Applicants' in the specification indicate that "the inventor has found….. could lead to a greater response towards SSRIs" (para 0042), "he present inventor has further surprisingly found …. could lead to a greater response towards SSRIs". However, the applicants' have not administered to patients any drugs claimed and shown such effects. There is no data or examples to show administration of pipamperone with an SSRI compound to a patient in treating an anxiety disorder or augmentation of the therapeutic effects of said SSRI compounds. Accordingly, the rejection is maintained.

Applicant's arguments regarding that Dipiperon teaches away from the use of pipamperone with a drug such as citalopram have been fully considered . Applicants'

state that specifically, on page 3, lines 9-11, Dipiperon teaches: "The simultaneous use of other antipsychotics, ... antidepressants ...increases the risk of the occurrence of tardive dyskinesia. However, it is deemed that the Dipiperon reference does not reach the level of a teaching away from combining pipamperone with any of the SSRI drugs claimed as suggested by Applicant. The Dipiperon document states that simultaneous use of other antipsychotics, ... antidepressants.. increases the risk of the occurrence of tardive dyskinesia and does not specifically teach the adverse effects are with the SSRI drugs claimed. Applicants' argue that Sanchez provide no explicit teaching or motivation to combine escitalopram with another drug and neither of the references provide any motivation to combine administration of citalopram with pipamperone. In response, Diperon teaches the use of pipamperone in the treatment of anxiety disorder and Sanchez teaches the use of citalopram in the treatment of anxiety disorders. Hence one of ordinary skill in the art would have been motivated to use pipamperone and citalopram in a combination therapy for the treatment of a disease or a disorder such as anxiety disorder due to expectation of synergistic effects and therapeutic benefits as both the compounds have been shown to be useful in a method of treatment of condition like anxiety disorder. With regards to the claims of both the drugs in the same composition, One of ordinary skill in the art would have been motivated to incorporate the both the agents herein in a single pharmaceutical composition because combining the agents herein each of which is known to be useful to treat anxiety disorders individually into a single composition useful for the very same purpose is *prima facie* obvious. See *In re Kerkhoven* 205 USPQ 1069. It is well known that it is

prima facie obvious to combine two or more ingredients each of which is taught by the prior art to be useful for the same purpose in order to form a third composition which is useful for the same purpose. The idea for combining them flows logically from their having been used individually in the prior art. *In re Sussman,* 1943 C.D. 518; *In re Pinten,* 459 F.2d 1053, 173 USPQ 801 (CCPA 1972); *In re Susi,* 58 CCPA 1074, 1079-80; 440 F.2d 442,445; 169 USPQ 423, 426 (1971); *In re Crockett,* 47 CCPA 1018, 1020-21; 279 F.2d 274, 276-277; 126 USPQ 186, 188 (1960). Thus, since the individual components are known to be used individually in the art for the same purpose, then to use them together as such or in one composition is obvious.

Applicants' argue that Dipiperon teaches away from the dose range of 5-15 mg /day and teaches an initial dose of 40-80 mg/day. There is no teaching or suggestion in the cited references to administer pipamperone at a lower dose than the recommended dose. In response, the Dipiperon does not teach one away from using 5-15 mg/day. The reference teach that dipiperon potentiates hypnotics and analgesics so that they can be given at a lower dose. Hence it would have been obvious to one of ordinary skill in the art at the time of the invention to try giving lower dosages of pipamperone when given in combination therapy.

Conclusion

No claims are allowed.

Applicant's amendment and addition of new claims necessitated the modified rejection presented in this Office action. Accordingly, THIS ACTION IS MADE FINAL.

See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Umamaheswari Ramachandran whose telephone number is 571-272-9926. The examiner can normally be reached on M-F 8:30 AM - 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on 571-272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/SREENI PADMANABHAN/

Supervisory Patent Examiner, Art Unit 1617